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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Chiron Corporation
Intellectual Property R440
PO Box 8097
Emeryville, CA 94662-8097

EXAMINER
NGUYEN, QUANG

ART UNIT	PAPER NUMBER
1636	11

DATE MAILED: 07/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/762,693	WILLIAMS ET AL.	
	Examin r	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover she t with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-16,26,30,31,36,38 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-25, 27-29, 32-35, 37 and 39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed on April 17, 2003 has been entered as Paper No. 10.

Claims 1-40 are pending in the present application.

Applicant's election without traverse of Group III (claims 17-29, 32-35, 37 and 39) in Paper No. 9 is acknowledged. Applicants further elected without traverse the following species: (a) dendritic cell as an antigen presenting cell, (b) neomycin as a selectable marker, (c) cancer cell as the target cell, and (d) IL-2 as the immunomodulatory cofactor.

Claims 1-16, 26, 30-31, 36, 38 and 40 are withdrawn from further consideration because they are drawn to the non-elected inventions and non-elected species.

Accordingly, claims 17-25, 27-29, 32-35, 37 and 39 are examined on the merits herein.

Claim Objections

Claims 18, 24, 27-29, 32-35, 37 and 39 are objected to because they contain embodiments of non-elected inventions and non-elected species. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-18, 20-22, 25, 27-29, 32-35, 37 and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification with respect to the elected invention, while being enabling for a method of producing a dendritic cell that presents an array of antigens comprising: (a) comparing first nucleic acid sequences expressed by a cancer cell population with second nucleic acid sequences expressed by a non-cancer cell population; (b) selecting nucleic acid sequences preferentially expressed by said cancer cell population relative to said non-cancer cell population; and (c) genetically modifying a dendritic cell to express the selected nucleic acid sequences, and wherein said cancer cell population and said non-cancer cell population are of the same tissue of origin; a dendritic cell produced by the same method; a method of activating T cells comprising contacting a T cell with an effective amount of genetically modifying autologous dendrtitic cells produced by the same method and a method of killing a cancer cell in a subject comprising administering to said subject an effective amount of genetically modifying autologous dendritic cells produced by the same method,

does not reasonably provide enablement for a method of producing a dendritic cell that presents an array of antigens comprising a step of genetically modifying a dendritic cell to express selected nucleic acid sequences preferentially expressed by a cancer cell population relative to any non-cancer cell population, a dendritic cell produced by the same method and methods of activating T cells and killing cancer cells in a subject using genetically modified allogeneic or xenogeneic dendritic cells produced

by the same method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, claims 17-18, 20-22, 25 and 27 are drawn to a method of producing a dendritic cell that presents an array of cancer cell antigens by genetically modifying the dendritic cell to express nucleic acid sequences preferentially expressed by a cancer cell population relative to a non-cancer cell population, and a dendritic cell produced by the same method. Claims 28-29 and 32-35 are drawn to a method of activating T cells comprising contacting a T cell with the same dendritic cell produced by the present invention. Claims 37 and 39 are directed to a method of killing or treating cancer cells comprising administering the dendritic cell produced by the present invention into a subject.

The instant specification is not enabled for the instant broadly claimed invention for the reasons discussed below.

(1) The breadth of the claims. The instant claims encompass a method of genetically modifying a dendritic cell to express nucleic acid sequences preferentially

expressed by a cancer cell population relative to any non-cancer cell population which is not necessarily from the same tissue of origin of the cancer cell population, a dendritic cell produced by the same method and methods of uses using the same genetically modified dendritic cells. With respect to claims 28-29 and 32-35, they encompass a method for activating a T cell *in vivo* or *ex vivo* with a genetically modifying autologous, allogeneic or xenogeneic dendritic cell. Claims 37 and 39 encompass a method of killing or treating a cancer cell comprising administering to a subject a genetically modifying autologous, allogeneic or xenogeneic dendritic cell produced by the present invention.

(2) The state and unpredictability of the prior art. At the effective filing date of the present application, little is known about the identification of genes or nucleic acid sequences encoding tumor antigens by comparing nucleic acid sequences preferentially expressed by a cancer cell population relative to a non-cancer cell population that is not derived from the same tissue of origin of the cancer cell population (Tuting et al. J. Mol. Med. 75:478-491, 1997, see the section on "Identification of genes encoding tumor antigens recognized by T cells" on page 483) or the use of allogeneic or xenogeneic genetically modified dendritic cells for activating T cells *in vivo* or *ex vivo* for the purpose of killing or treating a cancer (Tuting et al., see the section on "The role of specialized APC in the induction of T cell mediated tumor immunity" on page 485). Additionally, it should be noted that the physiological art is recognized to be unpredictable, particularly for obtaining therapeutic effects via immunotherapy involving the activation of T lymphocytes by the genetically modified dendritic cells of the present invention.

(3) The amount of direction or guidance provided. The instant specification fails to provide sufficient guidance for a skilled artisan on how to make and use the instant broadly claimed invention, particularly in the absence of any relevant examples (not prophetic examples as presented in the specification) dealing with the aforementioned issues that are not taught in the prior art. Without the sufficient guidance provided by the present application, then how does a skilled artisan know which nucleic acids preferentially expressed by a cancer cell population relatively to a non-cancer cell population that is not derived from the same tissue of origin are tumor-specific nucleic acids and not tissue specific nucleic acids? And which nucleic acid sequences are selected for genetically modifying the dendritic cells? Nor does the present disclosure provide any guidance for a skilled artisan on how to overcome adverse immune responses against genetically modified allogeneic or xenogeneic dendritic cells. It is unclear whether the allogeneic or xenogenic dendritic cells expressing an array of cancer antigens can withstand the adverse immune responses for a sufficient period of time for activating an effective amount of T cell activation *ex vivo* or *in vivo* to yield the desired therapeutic effects contemplated by Applicants (e.g., killing or treating a cancer in a subject).

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues raised above, the unpredictability of the relevant physiological art, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-25, 27-29, 32-35, 37 and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 17 and its dependent claims, the limitation "selecting at least one nucleic acid sequence" recited in step (b) is not consistent with the limitation "to express the selected nucleic acid sequences" recited in step (c). This is because if one nucleic acid sequence is selected, then it is unclear how a genetically modifying dendritic cell can express multiple selected nucleic acid sequences (as recited in step (c)) or an array of antigens as recited in the preamble of the claim. The metes and bounds of the claims are not clearly determined.

Claim 23 recites the limitation "the nucleic acid sequence" in line 1 of the claim. There is insufficient antecedent basis for this limitation in the claim. This is because in claim 17 from which claim 23 is dependent upon, selected nucleic acid sequences are recited. Therefore, it is unclear which nucleic acid sequence in claim 23 is referred to. Additionally, the phrase "wherein the selected nucleic acid sequence further encodes at least one selectable marker" is also unclear. Do selected nucleic acid sequences preferentially expressed by target cell population or cancer cell population for the elected invention also encode a selectable marker? The metes and bounds of claim 23 and its dependent claims 24, 27-29, 32-35, 37 and 39 are therefore not clearly determined.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 17-22, 25, 27-29, 32-35, 37 and 39 are rejected under 35 U.S.C. 102(e) as being anticipated by Nair et al. (U.S. Patent No. 5,853,719).

With respect to the elected species, Nair et al. teach a method for producing an RNA-loaded antigen-presenting cell (APC) including a dendritic cell by introducing into an APC tumor derived RNA that includes tumor-specific RNA (col. 1, line 46-61). Nair et al. further teach that tumor-specific RNA can be prepared using art-known techniques such as subtractive hybridization against RNA from non-tumor cells to diminish the risk of generating an autoimmune response (col. 2, lines 4-8; col. 3, lines 55-62). Nair et al. also teach that the produced dendritic cells can be used to induce cytotoxic T lymphocytes (CTL) responses or proliferation *in vivo* and *ex vivo*, as well as a method for producing a cytotoxic T lymphocyte by contacting a T lymphocyte *in vitro* with an antigen-presenting cell that is loaded with tumor-derived RNA, and maintaining the T lymphocytes under conditions conducive to CTL proliferation, thereby producing a CTL

(col. 2, lines 36-60; col. 6, lines 19-21). Furthermore, Nair et al. teach a method of treating tumor formation in a patient by administering to the patient a therapeutically effective amount of APC loaded with tumor-derived RNA, wherein the APC are derived from the same patient or a matched donor (col. 12, lines 27-34). Additionally, Nair et al. teach that the administration of lymphokines such as IL-2 or IL-4 can also be included in the CTL and antigen-presenting cells therapies to enhance CTL proliferation (col. 13, lines 2-5).

Since tumor-specific RNA can be prepared using art-known techniques such as subtractive hybridization against RNA from non-tumor cells as taught by Nair et al., the tumor-specific RNA preferentially expressed by tumor cells is selected, and that the preparation of such tumor-specific RNA includes an enriched population containing a plurality of RNA messages preferentially expressed by tumor cells (Please note the definition of "tumor-specific RNA by Nair et al. to be meant an RNA sample that, relative to unfractionated tumor-derived RNA, has a high content of RNA that is preferentially present in a tumor cell compared to a non-tumor cell, col. 3, lines 40-43).

Accordingly, the teachings of Nair et al. meet all the limitation of the instant claims. Therefore, Nair et al. anticipate the presently claimed invention.

Claims 17-22, 25, 27-29, 32-35, 37 and 39 are rejected under 35 U.S.C. 102(a) as being anticipated by Nair et al. (WO 97/41210).

With respect to the elected species, Nair et al. (WO 97/41210) teach a method for producing an RNA-loaded antigen-presenting cell (APC) including a dendritic cell by

introducing into an APC tumor derived RNA that includes tumor-specific RNA (see abstract). Nair et al. further teach that tumor-specific RNA can be prepared using art-known techniques such as subtractive hybridization against RNA from non-tumor cells to diminish the risk of generating an autoimmune response (page 3, lines 7-12). Nair et al. also teach that the produced dendritic cells can be used to stimulate cytotoxic T lymphocytes (CTL) proliferation *in vivo* and *ex vivo* (page 2, lines 11-14). Nair et al. also teach that if desired, RNA encoding an immunomodulator (e.g., IL-2, IL-1, IL-12) can also be introduced into the APC loaded with tumor-derived RNA to enhance the therapeutic effect of the RNA-loaded APCs (page 4, lines 9-17). Furthermore, Nair et al. teach a method of treating tumor formation in a patient by administering to the patient a therapeutically effective amount of APC loaded with tumor-derived RNA, wherein the APC are derived from the same patient or a matched donor (page 5, lines 18-24). Additionally, Nair et al. teach that the administration of lymphokines such as IL-2 or IL-4 can also be included in the CTL and antigen-presenting cells therapies to enhance CTL proliferation (page 30, line 33 continues to line 3 of page 31).

Since tumor-specific RNA can be prepared using art-known techniques such as subtractive hybridization against RNA from non-tumor cells as taught by Nair et al., the tumor-specific RNA preferentially expressed by tumor cells is selected, and that the preparation of such tumor-specific RNA includes an enriched population containing a plurality of RNA messages preferentially expressed by tumor cells (Please note the definition of "tumor-specific RNA by Nair et al. to be meant an RNA sample that, relative

to unfractionated tumor-derived RNA, has a high content of RNA that is preferentially present in a tumor cell compared to a non-tumor cell, page 8, lines 27-30).

Accordingly, the teachings of Nair et al. (WO 97/41210) meet all the limitation of the instant claims. Therefore, Nair et al. (WO 97/41210) anticipate the presently claimed invention.

Claims 17-20, 25, 27-29 and 33 are rejected under 35 U.S.C. 102(a) as being anticipated by Tuting et al. (J. Immunology 160:1139-1147, 1998).

Tuting et al. teach a method of preparing autologous human monocyte-derived dendritic cells transfected transiently with plasmid vectors encoding human MART-1/Melan-A, Pmel-17/gp100, tyrosine, MAGE-1 and MAGE-3 by particle bombardment and the transfected dendritic cells were used to stimulate autologous PBMC responder T cells (see abstract, and page 1142, section entitled "Autologous DC transfected with five different melanoma Ag cDNAs elicit Ag- and tumor-reactive CTL *in vitro*").

As the expression plasmids encoding the human melanoma Ags MART-1/Melan-A, Pmel-17/gp100, tyrosine, MAGE-1 and MAGE-3 were selected and utilized by Tuting et al. for transfecting autologous human dendritic cells, comparison nucleic acid sequences expressed by melanoma cells with nucleic acid sequences expressed by non-melanoma cells has been made.

Accordingly, the teachings of Tuting et al. meet all the limitation of the instant claims. Therefore, Tuting et al. anticipate the presently claimed invention.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gerald Leffers, Jr., Ph.D., may be reached at (703) 305-6232, or SPE, Remy Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.

Gerald D. Leffers Jr.
PATENT EXAMINER
Gerald G. Leffers Jr
A.U. 1636